Unexpected outcome (positive or negative) including adverse drug reactions

Upper gastrointestinal bleeding in a patient receiving selective serotonin reuptake inhibitor

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Summary

An older woman presented to the hospital with abdominal pain and subsequently had three episodes of melaena, requiring blood transfusions. She was known to suffer with severe depression and was on high-dose fluoxetine. Gastroscopy and colonoscopy failed to reveal an underlying cause for gastrointestinal (GI) bleeding. Possibility of high-dose selective serotonin reuptake inhibitors causing GI bleed was raised. Fluoxetine was discontinued and the patient was commenced on mirtazapine. The patient had no further GI bleeding and had significant improvement in haemoglobin.

BACKGROUND

Depression and the use of selective serotonin reuptake inhibitor (SSRI) are common in the older population. Iron deficiency anaemia is also common in this group. Potential adverse effects of SSRI on platelet function and risk of bleeding complication is not well known. Awareness of this side effect will help prevent bleeding complications and morbidity in high-risk patients.

CASE PRESENTATION

A 79-year-old woman presented with a 2-day history of vomiting and abdominal pain. She was admitted from a rehabilitation unit outside the catchment area of the admitting hospital. She was known to suffer from severe depression with multiple suicide attempts in the past. There was history of chronic back pain, gastro-oesophageal reflux disease and hypothyroidism. Her community psychiatrist had increased her dose of fluoxetine from 40 mg to 60 mg daily, few weeks prior to admission and her symptoms of depression was poorly controlled. Apart from fluoxetine, she was on diazepam 2 mg three times daily, ranitidine 150 mg twice daily and levothyroxine 100 mcg once a day.

INVESTIGATIONS

Systematic examination was unremarkable and there were no signs of an acute abdomen. She was not feverish and haemodynamically stable. Blood tests revealed a normal full blood count, renal and liver function. Thyroid function tests confirmed that she was biochemically euthyroid and compliant with her thyroid replacement therapy. Chest and abdominal radiograph were unremarkable. Culture of stool did not reveal any organisms and was negative for *Clostridium difficile* toxin. Blood and urine culture showed no growth.

The day after admission, the patient had an episode of melaena associated with a drop in haemoglobin (Hb) from 11 g/dl to 7 g/dl. Following transfusion of three units of packed cells, an oesophagoduodenoscopy revealed

grade III oesophagitis without any obvious bleeding or ulcer. Oesophagitis was deemed an unlikely source for significant upper gastrointestinal (GI) haemorrhage.

She remained stable for a further 2 weeks but subsequently had two further episodes of frank melaena associated with a drop in Hb to 8 g/dl. Colonoscopy revealed mild diverticular disease but failed to elucidate a cause of bleeding.

TREATMENT

The possibility of SSRI induced platelet dysfunction leading to GI bleeding was raised and fluoxetine was discontinued immediately.

As the patient was transferred outside the catchment area of the prescriber, she was reviewed by the inpatient psychiatric team in the hospital. A trial without fluoxetine was favoured and she was commenced on mirtazapine. Platelet function or clotting time was not assessed as the patient was taken off fluoxetine as soon as the association of GI haemorrhage was established.

Fluoxetine 60 mg was still continued after the first episode of GI bleed as the patient was exhibiting symptoms of severe depression and self harm. She attempted suffocating herself with pillows and required close monitoring. It was deemed inappropriate to discontinue or reduce the dose of fluoxetine as it had only recently been increased by the psychiatric team in the community.

OUTCOME AND FOLLOW-UP

There was no further GI bleeding. The patient's Hb improved to 11.5 g/dl and she remained stable over the next 2 months until she was discharged to an inpatient rehabilitation unit.

DISCUSSION

GI haemorrhage is a significant cause of morbidity and mortality in the British general population. Studies have reported an incidence of 103 / 100 000.¹ An important

contributor of risk for GI haemorrhage is adverse events associated with medications. Recent work has suggested that use of SSRI is associated with an increased risk of GI haemorrhage.²⁻⁸

SSRIs are most widely prescribed antidepressants and are widely used in older patients. According to one survey 14 million prescriptions were dispensed in the community in 2003.⁹ NICE guidelines recommend SSRIs to be the first line of treatment in patients with moderate depression.¹⁰

Serotonin or 5-hydroxytryptamine is synthesised in the serotonergic neurons in the central nervous system. Nearly 90% of serotonin is stored within the enterochromaffin cells in the GI tract and aids gut motility.

Serotonin is also contained within platelets and is released in response to vascular injury, which in turn promotes vasoconstriction and change in the shape of platelets that leads to aggregation.³ However, the serotonin contained within platelets is not synthesised locally and is taken up via selective serotonin reuptake transporters. These transporters have similar conformations to those present on serotonergic neurons in the central nervous system. SSRIs prevent serotonin reuptake in platelets, which in prolonged use, can lead to depletion of platelet serotonin. This reduces ability of the platelets to form clots and subsequently increases the risk of bleeding.

There have been reports of an increase in haemorrhagic complications among regular SSRIs users.²⁻⁸ Multiple studies have shown that SSRI use is specifically associated with an increase in the risk of developing serious GI bleeding, though the magnitude of this risk detected in different studies has been variable. The increased risk appears to correlate with the affinity of SSRI for SSRI receptor,^{2-4 11} and this was the reason for switching our patient from fluoxetine, high affinity to mirtazapine, low affinity. (table 1).

The increased risk of GI bleeding may be more pronounced in subjects with concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin. The mechanisms by which NSAIDs and SSRI are associated with GI bleeding are different. Aspirin and NSAIDs not only directly damage the GI mucosa, but also cause platelet dysfunction, while SSRIs reduce the effectiveness of the normal clotting mechanism. The absolute additional risk of an upper GI bleed requiring hospital admission, with an SSRI prescribed alone is about one in 300 patient years, but co-prescription of SSRIs with aspirin increases the risk to 1 in 200 and with NSAIDs to 1 in 80.² The risk with a non-steroidal drug alone is 1 in 200.¹²

SSRIs are frequently used for major depressive disorders but only 50–60% of patients respond to a standard dose. For non-responders, dose escalation is often applied, particularly in late-life depression.¹³ In our patient, the temporal relationship between the increment of fluoxetine dose and GI bleeding, more than once, is impressive. However, the prompt resolution of the symptoms and improvement in Hb with discontinuation of SSRI therapy further strengthened our suspicion to the cause. The authors, however, acknowledge the limitations in establishing the causality.

Acid suppression therapy with a proton pump inhibitor (PPI) is advised for those who are considered high risk, especially when concomitant use of NSAIDs or aspirin therapy is unavoidable.¹⁴ Two studies have found risk of GI bleeding among SSRI users reduced through concomitant

Table 1 Antidepressants and affinity for selective serotonin reuptake transporters³⁻⁵

Affinity	Antidepressants
High	Clomipramine Fluoxetine Sertraline Paroxetine
Intermediate	Citalopram Fluvoxamine Venlafaxine
Low	Doxepin Mirtazapine Moclobemide Nortriptyline

use of acid suppression therapy, one of which confirmed the risk to be almost eliminated with PPI co-therapy.^{7 8}

In conclusion, caution is advised in prescribing SSRIs to patients with history or risk factors for GI bleed. Low-affinity SSRIs should be considered in patients where discontinuation of SSRI is not advised.

Learning points

- ▶ SSRIs are widely prescribed, especially in the older population.
- ▶ They prevent serotonin uptake in platelets and thus reduce their ability to form clots.
- ▶ Caution should be exercised in prescribing SSRI for patients who are at high risk of bleeding particularly with concurrent use of NSAIDs and aspirin.
- ▶ Addition of PPI therapy should be considered for those who are at high risk of GI bleed.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Rockall TA**, Logan RF, Devlin HB, *et al*. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and Members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. *BMJ* 1995;**311**:222–6.
2. **Dalton SO**, Johansen C, Mellemkjaer L, *et al*. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch Intern Med* 2003;**163**:59–64.
3. **de Abajo FJ**, Rodríguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ* 1999;**319**:1106–9.
4. **Meijer WE**, Heerdink ER, Nolen WA, *et al*. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. *Arch Intern Med* 2004;**164**:2367–70.
5. **van Walraven C**, Mamdani MM, Wells PS, *et al*. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ* 2001;**323**:655–8.
6. **Serebruany VL**. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? *Am J Med* 2006;**119**:113–16.
7. **Dall M**, Schaffalitzky de Muckadell OB, Lassen AT, *et al*. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2009;**7**:1314–21.
8. **Targownik LE**, Bolton JM, Metge CJ, *et al*. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. *Am J Gastroenterol* 2009;**104**:1475–82.
9. Department of Health. Prescribing Analysis and Cost Data, 2005. www.publications.doh.gov.uk/stats/pca2003.htm (accessed 10 January 2005).

10. National Institutes for Clinical Effectiveness. *Treatment Guideline for Depression*. London: NICE, 2004. www.nice.org.uk (accessed 10 January 2011).
11. **Looper KJ**. Potential medical and surgical complications of serotonergic antidepressant medications. *Psychosomatics* 2007;**48**:1–9.
12. **Po AL**. Antidepressants and upper gastrointestinal bleeding. *BMJ* 1999;**319**:1081–2.
13. **Lotrich FE**, Pollock BG, Kirshner M, *et al*. Serotonin transporter genotype interacts with paroxetine plasma levels to influence depression treatment response in geriatric patients. *J Psychiatry Neurosci* 2008;**33**:123–30.
14. North of England Dyspepsia Guideline Development Group. *Dyspepsia: Managing Dyspepsia in Adults in Primary Care*. Centre for Health Services Research, Report No. 112. Newcastle: University of Newcastle, 2004.

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